Handbook of Pharmaceutical Excipients

FOURTH EDITION

Edited by

Raymond C Rowe

BPharm, PhD, DSc, FRPharmS, CChem, FRSC, CPhys, MInstP

Senior Principal Scientist

AstraZeneca

Macclesfield, UK

Paul J Sheskey

BSc, RPh

Technical Service Leader

Water Soluble Polymers R&D

The Dow Chemical Company

Midland

MI, USA

Paul J Weller

BSc, MSc, CChem, MRSC

Publisher – Science and Practice

Royal Pharmaceutical Society of Great Britain

London, UK

London • Chicago Pharmaceutical Press

APhA American Pharmaceutical Association

Published by the Pharmaceutical Press
Publications division of the Royal Pharmaceutical Society of Great Britain

1 Lambeth High Street, London SE1 7JN, UK
100 South Atkinson Road, Suite 206, Grayslake, IL 60030-7820, USA

and the American Pharmaceutical Association
2215 Constitution Avenue NW, Washington, DC 20037-2985, USA

First edition published 1986
Second edition published 1994
Third edition published 2000
Fourth edition published 2003

Text design by Barker Hilsdon, Lyme Regis
Typeset by Bibliocraft Ltd, Dundee
Printed in Great Britain by The Bath Press, Bath

ISBN 0 85369 472 9 (UK)
ISBN 1 58212 022 6 (USA)

A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
Handbook of pharmaceutical excipients.– 4th ed. / edited by Raymond C. Rowe, Paul J. Sheskey, Paul J. Weller.
p. ; cm.
Includes bibliographical references and index.
ISBN 1-58212-022-6 (alk. paper) – ISBN 0-85369-472-9 (alk. paper)
1. Excipients–Handbooks, manuals, etc.
[DNLM: 1. Excipients–Handbooks. QV 735 H236 2003] I. Rowe, Raymond C. II. Sheskey, Paul J. III. Weller, Paul J.

RS201.E87H36 2003
615'.19–dc21

2003002641

Crospovidone

1 Nonproprietary Names

BP: Crospovidone
PhEur: Crospovidonum
USPNF: Crospovidone

2 Synonyms

Crosslinked povidone; E1202; *Kollidon CL*; *Kollidon CL-M*; *Polyplasdone XL*; *Polyplasdone XL-10*; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

3 Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4 Empirical Formula Molecular Weight

$(C_6H_9NO)_n$ >1 000 000

Crospovidone is a water-insoluble synthetic crosslinked homopolymer of *N*-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

5 Structural Formula

See Povidone.

6 Functional Category

Tablet disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods.[1–4] It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets.[5] Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

8 Description

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for crospovidone.

Test	PhEur 2002	USPNF 20 (Suppl 1)
Identification	+	+
Characters	+	—
pH (1% suspension)	—	5.0–8.0
Water	—	≤5.0%
Residue on ignition	≤0.1%	≤0.4%
Water-soluble substances	≤1.0%	≤1.5%
Peroxides	≤400 ppm	—
Heavy metals	≤10 ppm	≤0.001%
Vinylpyrrolidinone	—	≤0.1%
Loss on drying	≤5.0%	—
Nitrogen content (anhydrous basis)	11.0–12.8%	11.0–12.8%

10 Typical Properties

Acidity/alkalinity: pH = 5.0–8.0 (1% w/v aqueous slurry)
Density: 1.22 g/cm^3
Density (bulk): *see* Table II.
Density (tapped): *see* Table II.

Table II: Density values of commercial grades of crospovidone.

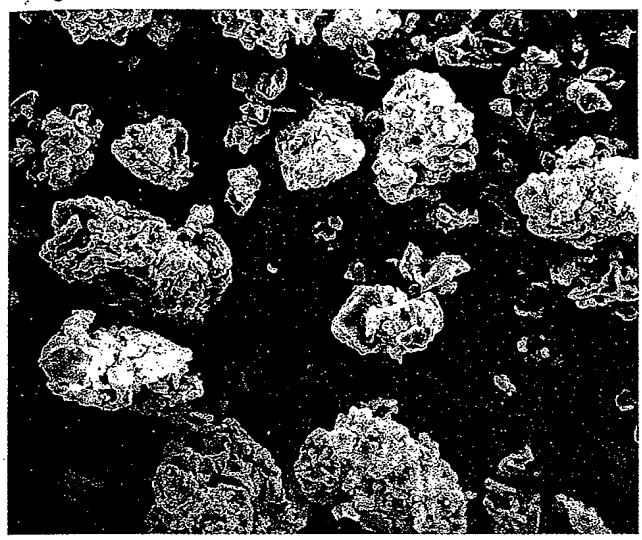
Commercial grade	Density (bulk) g/cm^3	Density (tapped) g/cm^3
Kollidon CL	0.3–0.4	0.4–0.5
Kollidon CL-M	0.15–0.25	0.3–0.5
Polyplasdone XL	0.213	0.273
Polyplasdone XL-10	0.323	0.461

Moisture content: maximum moisture sorption is approximately 60%.
Particle size distribution: less than 400 µm for *Polyplasdone XL*; less than 74 µm for *Polyplasdone XL-10*. Approximately 50% greater than 50 µm and maximum of 3% greater than 250 µm in size for *Kollidon CL*. Minimum of 90% of particles are below 15 µm for *Kollidon CL-M*.
Solubility: practically insoluble in water and most common organic solvents.
Specific surface area: *see* Table III.

Table III: Specific surface areas for commercial grades of crospovidone.

Commercial grade	Surface area (m^2/g)
Kollidon CL	1.0
Kollidon CL-M	3.0–6.0
Polyplasdone XL	0.6–0.8
Polyplasdone XL-10	1.2–1.4

SEM 1
Excipient: Crospovidone (*Polyplasdone XL-10*)
Manufacturer: ISP Corp.
Lot No.: S81031
Magnification: 400×
Voltage: 10 kV



11 Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials; *see* Povidone.

13 Method of Manufacture

Acetylene and formaldehyde are reacted in the presence of a highly active catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer vinylpyrrolidone is then polymerized in solution, using a catalyst. Crospovidone is prepared by a 'popcorn polymerization' process.

14 Safety

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short-term animal toxicity studies have shown no adverse effects associated with crospovidone.[6] However, owing to the lack of available data, an acceptable daily intake in humans has not been specified by the WHO.[6]

LD_{50} (mouse, IP): 12 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets; topical, transdermal, and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Povidone.

18 Comments

Crospovidone has been studied as a superdisintegrant. The ability of the compound to swell has been examined directly using scanning electron microscopy.[7] The impact of crospovidone on percolation has also been examined.[8] The impact of crospovidone on dissolution of poorly soluble drugs in tablets has also been investigated.[9]

19 Specific References

1 Kornblum SS, Stoopak SB. A new tablet disintegrating agent: crosslinked polyvinylpyrrolidone. *J Pharm Sci* 1973; 62: 43–49.
2 Rudnic EM, Lausier JM, Chilamkurti RN, Rhodes CT. Studies of the utility of cross linked polyvinylpolypyrrolidine as a tablet disintegrant. *Drug Dev Ind Pharm* 1980; 6: 291–309.
3 Gordon MS, Chowhan ZT. Effect of tablet solubility and hygroscopicity on disintegrant efficiency in direct compression tablets in terms of dissolution. *J Pharm Sci* 1987; 76: 907–909.
4 Gordon MS, Rudraraju VS, Dani K, Chowhan ZT. Effect of the mode of super disintegrant incorporation on dissolution in wet granulated tablets. *J Pharm Sci* 1993; 82: 220–226.
5 Schiermeier S, Schmidt PC. Fast dispersible ibuprofen tablets. *Eur J Pharm Sci* 2002; 15(3): 295–305.
6 FAO/WHO. Evaluation of certain food additives and contaminants. Twenty-seventh report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1983; No. 696.
7 Thibert R, Hancock BC. Direct visualization of superdisintegrant hydration using environmental scanning electron microscopy. *J Pharm Sci* 1996; 85: 1255–1258.
8 Caraballo I, Fernandez-Arevalo M, Millan M, *et al.* Influence of disintegrant on the drug percolation threshold in tablets. *Drug Dev Ind Pharm* 1997; 23(7): 665–669.
9 Yen SY, Chen CR, Lee MT, Chen LC. Investigation of dissolution enhancement of nifedipine by deposition on superdisintegrants. *Drug Dev Ind Pharm* 1997; 23(3): 313–317.

20 General References

Barabas ES, Adeyeye CM. Crospovidone. In: Brittain HG, ed. *Analytical Profiles of Drug Substances and Excipients*, vol. 24. London: Academic Press, 1996: 87–163.
BASF. Technical literature: *Insoluble Kollidon grades*, 1996.
ISP. Technical literature: *Polyplasdone crospovidone NF*, 1999.
Wan LSC, Prasad KPP. Uptake of water by excipients in tablets. *Int J Pharm* 1989; 50: 147–153.

21 Authors

X He, AH Kibbe.

22 Date of Revision

25 October 2002.

Povidone

1 Nonproprietary Names

BP: Povidone
JP: Povidone
PhEur: Povidonum
USP: Povidone

2 Synonyms

E1201; *Kollidon*; *Plasdone*; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2- pyrrolidinone polymer.

3 Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4 Empirical Formula Molecular Weight

$(C_6H_9NO)_n$ 2500–3 000 000

The USP 25 describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a *K*-value, ranging from 10 to 120. The *K*-value is calculated using Fikentscher's equation:[1]

$$\log z = c\left(\frac{75k^2}{1+1.5kc}\right)+k$$

where z is the relative viscosity of the solution of concentration c, k is the *K*-value $\times 10^{-3}$, and c is the concentration in % w/v.

Alternatively, the *K*-value may be determined from the following equation:

$$K\text{-value} \quad \sqrt{\frac{300c\log z(c+1.5c\log z)^2+1.5}{0.15c+0.003c^2}}$$

where z is the relative viscosity of the solution of concentration c, k is the *K*-value $\times 10^{-3}$, and c is the concentration in % w/v.

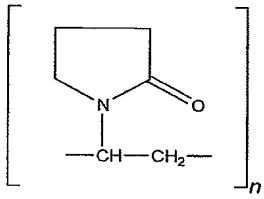
Approximate molecular weights for different povidone grades are shown in Table I.

Table I: Approximate molecular weights for different grades of povidone.

K-value	Approximate molecular weight
12	2 500
15	8 000
17	10 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

See also Section 8.

5 Structural Formula



6 Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.[2,3] Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.[4–6] Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone. *See* Table II.

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations; *see* Section 14.

Table II: Uses of povidone.

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5–5

8 Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with *K*-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher *K*-value povidones are manufactured by drum drying and occur as plates.

9 Pharmacopeial Specifications

See Table III.

Table III: Pharmacopeial specifications for povidone.

Test	JP 2001	PhEur 2002 (Suppl 4.3)	USP 25
Identification	+	+	+
Characters	—	+	—
pH	—	—	3.0–7.0
$K \leqslant 30$	3.0–5.0	3.0–5.0	—
$K > 30$	4.0–7.0	4.0–7.0	—
Appearance of solution	+	+	—
Viscosity	—	+	—
Water	⩽5.0%	⩽5.0%	⩽5.0%
Residue on ignition	⩽0.1%	⩽0.1%	⩽0.1%
Lead	—	—	⩽10 ppm
Aldehydes	⩽500 ppm[a]	⩽500 ppm[a]	⩽0.05%
Hydrazine	⩽1 ppm	⩽1 ppm	⩽1 ppm
Vinylpyrrolidinone	⩽10 ppm	⩽10 ppm	⩽0.2%
Peroxides	⩽400 ppm[b]	⩽400 ppm[b]	—
K-value	25–90	—	10–120
⩽15	90.0–108.0%	85.0–115.0%	85.0–115.0%
>15	90.0–108.0%	90.0–108.0%	90.0–108.0%
Heavy metals	⩽10 ppm	⩽10 ppm	—
Assay (nitrogen content)	11.5–12.8%	11.5–12.8%	11.5–12.8%

[a] Expressed as acetaldehyde.

[b] Expressed as hydrogen peroxide.

10 Typical Properties

Acidity/alkalinity: pH = 3.0–7.0 (5% w/v aqueous solution).
Density (bulk): 0.29–0.39 g/cm^3 for *Plasdone*.
Density (tapped): 0.39–0.54 g/cm^3 for *Plasdone*.
Density (true): 1.180 g/cm^3
Flowability:
20 g/s for povidone K-15
16 g/s for povidone K-29/32
Melting point: softens at 150°C.
Moisture content: povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities. *See* Figures 1 and 2.

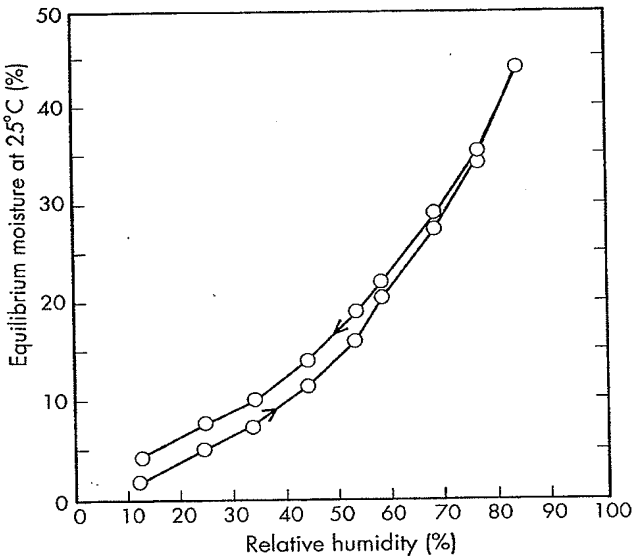


Figure 1: Sorption–desorption isotherm of povidone K-15 (*Plasdone K-15*).

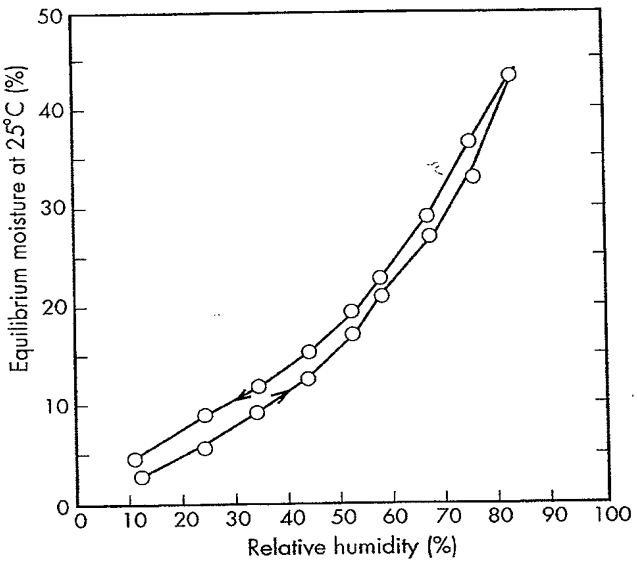


Figure 2: Sorption–desorption isotherm of povidone K-29/32 (*Plasdone K-29/32*).

Particle size distribution:
Kollidon 25/30: 90% >50 μm, 50% >100 μm, 5% >200 μm
Kollidon 90: 90% >200 μm, 95% >250 μm[7]

Solubility: freely soluble in acids, chloroform, ethanol, ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the *K*-value.

Viscosity (dynamic): the viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed. *See* Tables IV and V.[7]

Table IV: Dynamic viscosity of 10% w/v aqueous povidone (*Kollidon*) solutions at 20°C.[7]

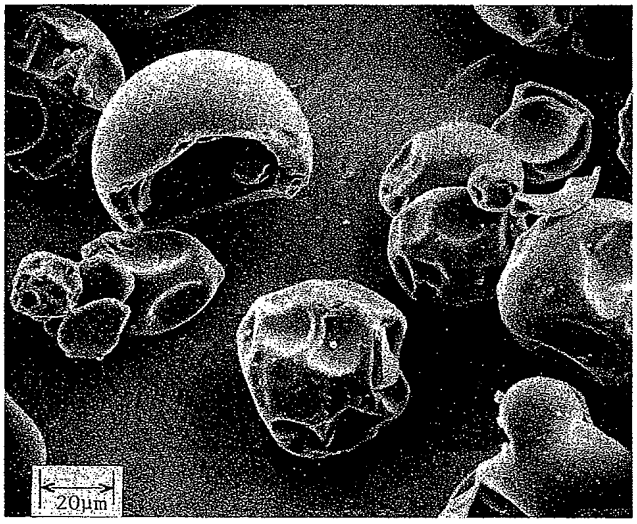
Grade	Dynamic viscosity (mPa s)
K-11/14	1.3–2.3
K-16/18	1.5–3.5
K-24/27	3.5–5.5
K-28/32	5.5–8.5
K-85/95	300–700

Table V: Dynamic viscosity of 5% w/v povidone (*Kollidon*) solutions in ethanol and propan-2-ol at 25°C.[7]

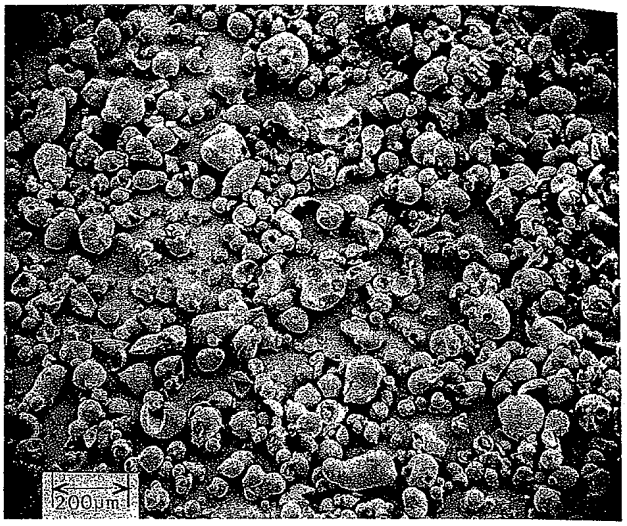
Grade	Dynamic viscosity (mPa s)	
	Ethanol	Propan-2-ol
K-12PF	1.4	2.7
K-17PF	1.9	3.1
K-25	2.7	4.7
K-30	3.4	5.8
K-90	53.0	90.0

SEM: 1
Excipient: Povidone K-15 (*Plasdone K-15*)
Manufacturer: ISP
Lot No.: 82A-1
Magnification: 60 ×
Voltage: 5 kV

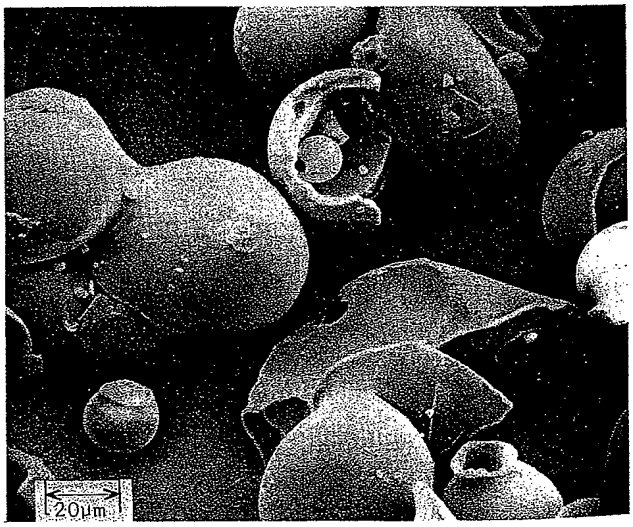
SEM: 2
Excipient: Povidone K-15 (*Plasdone K-15*)
Manufacturer: ISP
Lot No.: 82A-1
Magnification: 600 ×
Voltage: 5 kV



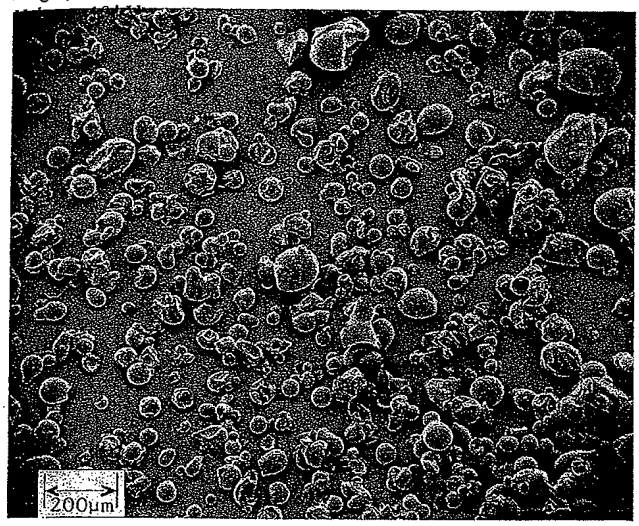
SEM: 3
Excipient: Povidone K-26/28 (*Plasdone K-26/28*)
Manufacturer: ISP
Lot No.: 82A-2
Magnification: 60 ×
Voltage: 5 kV



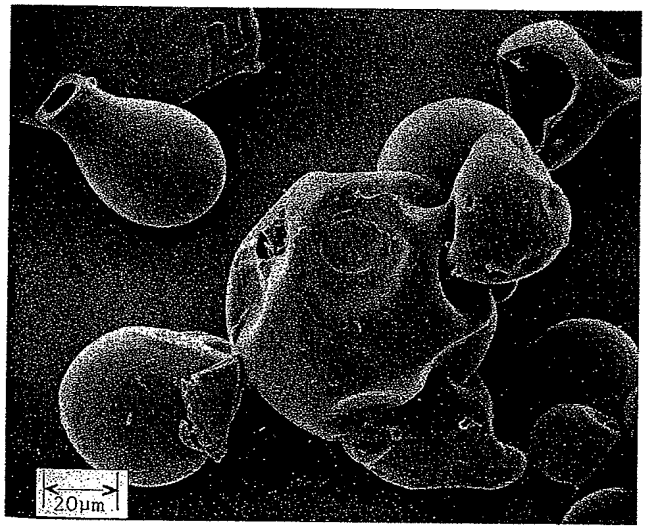
SEM: 4
Excipient: Povidone K-26/28 (*Plasdone K-26/28*)
Manufacturer: ISP
Lot No.: 82A-2
Magnification: 600 ×
Voltage: 10 kV



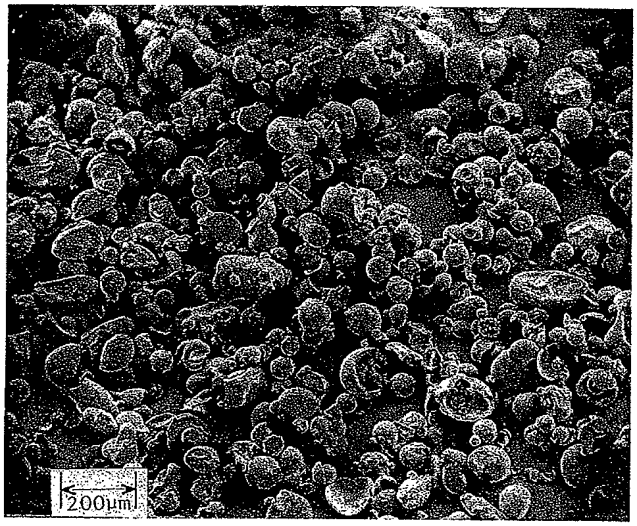
SEM: 5
Excipient: Povidone K-30 (*Plasdone K-30*)
Manufacturer: ISP
Lot No.: 82A-4
Magnification: 60 ×



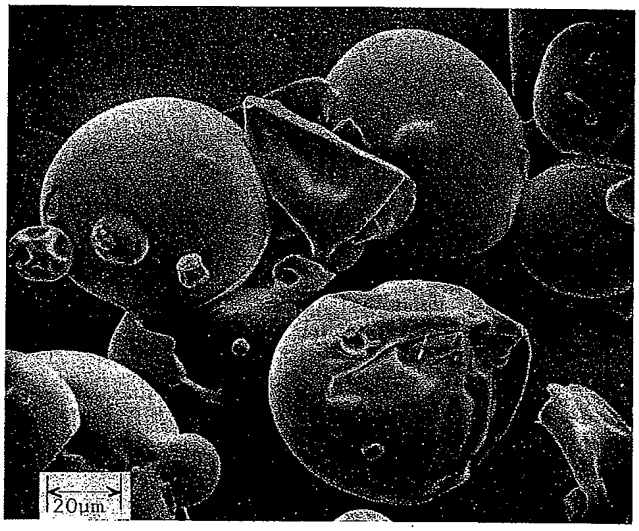
SEM: 6
Excipient: Povidone K-30 (*Plasdone K-30*)
Manufacturer: ISP
Lot No.: 82A-4
Magnification: 600 ×
Voltage: 10 kV



SEM: 7
Excipient: Povidone K-29/32 (*Plasdone K-29/32*)
Manufacturer: ISP
Lot No.: 82A-3
Magnification: 60 ×
Voltage: 5 kV



SEM: 8
Excipient: Povidone K-29/32 (*Plasdone K-29/32*)
Manufacturer: ISP
Lot No.: 82A-3
Magnification: 600 ×
Voltage: 10 kV



11 Stability and Storage Conditions

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties. Aqueous

solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds; *see* Section 18. The efficacy of some preservatives, e.g., thimerosal, may be adversely affected by the formation of complexes with povidone.

13 Method of Manufacture

Povidone is manufactured by the Reppe process. Acetylene and formaldehyde are reacted in the presence of a highly active copper acetylide catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer, vinylpyrrolidone, is then polymerized in the presence of a combination of catalysts to produce povidone.

14 Safety

Povidone has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander, although it has now been superseded for this purpose by dextran.[8]

Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.[8] Povidone additionally has no irritant effect on the skin and causes no sensitization.

Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site of intramuscular injections formulated with povidone.[9] Evidence also exists that povidone may accumulate in the organs of the body following intramuscular injection.[10]

A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight.[11]

LD_{50} (mouse, IP): 12 g/kg[12]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Accepted in Europe as a food additive. Included in the FDA Inactive Ingredients Guide (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspensions, and tablets; sublingual tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Crospovidone.

18 Comments

The molecular adduct formation properties of povidone may be used advantageously in solutions, slow-release solid-dosage forms, and parenteral formulations. Perhaps the best-known example of povidone complex formation is povidone–iodine, which is used as a topical disinfectant.

For accurate standardization of solutions, the water content of the solid povidone must be determined before use and taken into account for any calculations.

19 Specific References

1 Fikentscher H, Herrle K. Polyvinylpyrrolidone. *Modern Plastics* 1945; 23(3): 157–161, 212, 214, 216, 218.

2 Becker D, Rigassi T, Bauer-Brandl A. Effectiveness of binders in wet granulation: comparison using model formulations of different tabletability. *Drug Dev Ind Pharm* 1997; 23(8): 791–808.

3 Stubberud L, Arwidsson HG, Hjortsberg V, Graffner C. Water–solid interactions. Part 3. Effect of glass transition temperature, T_g and processing on tensile strength of compacts of lactose and lactose/polyvinyl pyrrolidone. *Pharm Dev Technol* 1996; 1(2): 195–204.

4 Iwata M, Ueda H. Dissolution properties of glibenclamide in combinations with polyvinylpyrrolidone. *Drug Dev Ind Pharm* 1996; 22: 1161–1165.

5 Lu WG, Zhang Y, Xiong QM, *et al.* Development of nifedipine (NE) pellets with a high bioavailability. *Chin Pharm J Zhongguo Yaoxue Zazhi* 1995; 30(Nov Suppl): 24–26.

6 Chowdary KP, Ramesh KV. Microencapsulation of solid dispersions of nifedipine-novel approach for controlling drug release. *Indian Drugs* 1995; 32(Oct): 477–483.

7 BASF Corporation. Technical literature: *Soluble Kollidon grades, soluble polyvinylpyrrolidone for the pharmaceutical industry*, 1997.

8 Wessel W, Schoog M, Winkler E. Polyvinylpyrrolidone (PVP), its diagnostic, therapeutic and technical application and consequences thereof. *Arzneimittelforschung* 1971; 21: 1468–1482.

9 Hizawa K, Otsuka H, Inaba H, *et al.* Subcutaneous pseudosarcomatous polyvinylpyrrolidone granuloma. *Am J Surg Pathol* 1984; 8: 393–398.

10 Christensen M, Johansen P, Hau C. Storage of polyvinylpyrrolidone (PVP) in tissues following long-term treatment with a PVP containing vasopressin preparation. *Acta Med Scand* 1978; 204: 295–298.

11 FAO/WHO. Evaluation of certain food additives and contaminants. Twenty-seventh report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1983; No. 696.

12 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 10th edn. New York: Wiley, 2000: 3015.

20 General References

Adeyeye CM, Barabas E. Povidone. In: Brittain HG, ed. *Analytical Profiles of Drug Substances and Excipients*, vol. 22. London: Academic Press, 1993: 555–685.

Horn D, Ditter W. Chromatographic study of interactions between polyvinylpyrrolidone and drugs. *J Pharm Sci* 1982; 71: 1021–1026.

Hsiao CH, Rhodes HJ, Blake MI. Fluorescent probe study of sulfonamide binding to povidone. *J Pharm Sci* 1977; 66: 1157–1159.

ISP. Technical literature: *Plasdone povidone USP*, 1999.

Jager KF, Bauer KH. Polymer blends from PVP as a means to optimize properties of fluidized bed granulates and tablets. *Acta Pharm Technol* 1984; 30(1): 85–92.

Plaizier-Vercammen JA, DeNève RE. Interaction of povidone with aromatic compounds III: thermodynamics of the binding equilibria and interaction forces in buffer solutions at varying pH values and varying dielectric constant. *J Pharm Sci* 1982; 71: 552–556.

Robinson BV, Sullivan FM, Borzelleca JF, Schwartz SL. *PVP: A Critical Review of the Kinetics and Toxicology of Polyvinylpyrrolidone (Povidone)*. Chelsea, MI: Lewis Publishers, 1990.

Shefter E, Cheng KC. Drug–polyvinylpyrrolidone (PVP) dispersions. A differential scanning calorimetric study. *Int J Pharm* 1980; 6: 179–182.

Smolinske SC. *Handbook of Food, Drug, and Cosmetic Excipients*. Boca Raton, FL: CRC Press, 1992: 303–305.

21 Author

AH Kibbe.

22 Date of Revision

30 October 2002.

THE PATENT AND TRADEMARK OFFICE IS RESPECTFULLY REQUESTED TO PLACE ITS STAMP ON THIS **POSTAL CARD** AND PLACE IT IN THE OUTGOING MAIL TO SHOW THE FOLLOWING PAPERS HAVE BEEN RECEIVED.

Via US First Class Mail

MAILING DATE: October 8, 2004 **LVM REFERENCE No.** 227833
APPLICATION OF: Sunami et al. **CLIENT:** Akros Pharma-JT
U.S. PATENT APPLICATION NO. 10/802,220
FILED: March 17, 2004
JKJ/brz
TITLE: PHARMACEUTICAL COMPOSITIONS OF CETP INHIBITORS

ENCLOSURES:
☒ Preliminary Amendment (10 pages);
☒ Substitute Specification (53 pages);
☒ Marked-up Version of Specification (55 pages);
☒ Information Disclosure Statement (4 pages in duplicate);
☒ Form PTO-1449 (4 pages);
☒ Copy of International Search Report (7 pages);
☒ Copies of References BY-EJ.

THE PATENT AND TRADEMARK OFFICE IS RESPECTFULLY REQUESTED TO PLACE ITS STAMP ON THIS **POSTAL CARD** AND PLACE IT IN THE OUTGOING MAIL TO SHOW THE FOLLOWING PAPERS HAVE BEEN RECEIVED.

Via US First Class Mail

MAILING DATE: October 8, 2004 **LVM REFERENCE No.** 227833
APPLICATION OF: Sunami et al. **CLIENT:** Akros Pharma-JT
U.S. PATENT APPLICATION NO. 10/802,220
FILED: March 17, 2004
JKJ/brz
TITLE: PHARMACEUTICAL COMPOSITIONS OF CETP INHIBITORS

ENCLOSURES:
☒ Preliminary Amendment (10 pages);
☒ Substitute Specification (53 pages);
☒ Marked-up Version of Specification (55 pages);
☒ Information Disclosure Statement (4 pages in duplicate);
☒ Form PTO-1449 (4 pages);
☒ Copy of International Search Report (7 pages);
☒ Copies of References BY-EJ.

KAS LLP